supplemental data, there are expanded opportunities for researchers to disseminate actual study data; this should facilitate independent evaluation by regulatory agencies.

As scientists specializing in regulatory safety evaluations, we have extensive experience in interpreting chemical toxicity studies from government, academia, and private-sector laboratories. In conducting chemical risk assessments, we believe that scientists from all sectors should support the use of objective criteria for determining data quality and study reliability (Schneider et al. 2009) coupled with a structured evaluative framework, such as that of the World Health Organization International Programme on Chemical Safety (Boobis et al. 2006, 2008), to provide a systematic approach for assessing the overall weight of the evidence for observed effects and the postulated mode of action. In this manner, data from laboratory experiments, epidemiological investigations, and cutting-edge mechanistic research from all relevant studies—GLP and non-GLP—and from all investigators, regardless of affiliation or funding source, can be comprehensively reviewed, given appropriate weight, and integrated in a manner that provides a robust, biologically plausible understanding of the potential hazards and risks that exposures to a substance could pose.

This letter has been reviewed in accordance with the peer- and administrative-review policies of the authors' organizations. The views expressed here are those of the authors and do not necessarily reflect the opinions and/or policies of their employers.

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ICCVAM: Not Doing Enough

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Anyone interested in the facts about the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and its ineffectiveness, rather than just another ICCVAM/National Toxicology Program (NTP) fluff piece (Birnbaum and Stokes 2010), should read the 2008 front page *Washington Post* exposé of ICCVAM (Gaul 2008) and the PETA report on which the *Post* investigation was based (PETA 2008).

Birnbaum and Stokes' "PR piece" notwithstanding, ICCVAM should be held responsible for failing to abide by its Congressional mandate to support the development and implementation of non-animal testing methods.

Sadly, it appears that the new leadership of the National Institute of Environmental Health Sciences is no more inclined to improve the quality of the science supporting regulatory decision-making than the previous one.

The author is employed by People for the Ethical Treatment of Animals, the largest animal rights organization in the world.

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ICCVAM: Birnbaum and Stokes Respond

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Sandler's comments about our editorial concerning the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) (Birnbaum and Stokes 2010) suggest a lack of awareness of the role and significance of the contributions of ICCVAM. The 2008 *Washington Post* article she cites (Gaul 2008) contained many inaccurate statements (a letter correcting the errors was submitted to the *Washington Post,* but it was not published). We appreciate this opportunity to provide accurate factual information about ICCVAM.

ICCVAM is a congressionally mandated committee that does not have laboratories and does not develop test methods or conduct validation studies. Rather, ICCVAM depends on other organizations, including its 15 member agencies, to carry out such activities. The director of the National Institute of Environmental Health Sciences (NIEHS) established ICCVAM in 1997, with the cooperation of 14 other agencies, in order to provide a coordinated interagency process to facilitate the regulatory acceptance of scientifically valid alternative methods. As an interagency forum, ICCVAM also coordinates and promotes related issues, including national and international harmonization, guidance on validation studies, and awareness of accepted alternative methods.

ICCVAM was formally established by legislation in 2000 with signing of the ICCVAM Authorization Act of 2000. This law charges ICCVAM to "review and evaluate new or revised or alternative test methods, … including the coordination of technical reviews of proposed new or revised or alternative test methods …." ICCVAM develops and submits recommendations based on its reviews to the Secretary of Health and Human Services for transmittal to federal agencies. Agencies must review the recommendations and respond to ICCVAM within 180 days. ICCVAM has implemented a transparent and scientifically rigorous evaluation process for test methods that has resulted in national and international regulatory acceptance of all recommended test methods. ICCVAM has contributed to the acceptance of 33 alternative test methods, including 17 based on formal comprehensive evaluations (ICCVAM 2010). Recommendations on an additional 4 methods are pending.

The National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) administers ICCVAM and provides scientific and operational support for ICCVAM activities. Consistent with the NTP

mission, NICEATM also conducts independent validation studies on new, revised, and alternative test methods, and coordinates international validation studies with its counterparts in Japan, Europe, and Canada (NIEHS 2009).

In 2008, NICEATM and ICCVAM launched a 5-year plan to further reduce, refine, and replace the use of animals in regulatory testing in conjunction with federal agencies and other stakeholders (ICCVAM 2008). The plan seeks to advance alternative test methods of high scientific quality that will continue to protect and advance the health of people, animals, and the environment. The plan emphasizes using new technology to develop predictive systems that will lessen or avoid the need for animals where scientifically feasible.

The NIEHS and NTP support research that may lead to the development of new test methods relevant to regulatory testing. These include the Tox21 collaboration between the NTP, the National Institutes of Health Chemical Genomics Center, and the U.S. Environmental Protection Agency (Schmidt 2009). The Tox21 initiative is the largest *in vitro* toxicology research program ever conducted worldwide and is expected to yield candidate methods and approaches with potential applicability to regulatory testing. Following standardization and validation in consultation with ICCVAM, methods with regulatory applicability will be reviewed by ICCVAM and recommendations forwarded to appropriate agencies.

ICCVAM has been enormously successful in gaining regulatory acceptance of alternative methods (ICCVAM 2010). Gaining regulatory acceptance requires high-quality studies that prove that the alternative test methods will provide the same or better level of protection of workers and consumers as the methods they might replace. The test method must also be shown to be reproducible in different laboratories.

The animal welfare benefits of ICCVAM's work are evidenced by many examples. These include an alternative test for acute oral toxicity that has replaced the LD_{50} test (median lethal dose), which used as many as 200 animals per test, with the Up-and-Down Procedure (UDP), which uses only 7 animals on average per test (NIEHS 2001; Organisation for Economic Co-operation and Development 2008). The UDP and other alternative test methods have profoundly reduced animal use for acute oral toxicity testing, which is conducted to determine the poisoning potential of chemicals and products and is the most commonly conducted safety test worldwide.

Another landmark ICCVAM contribution is the reduction and refinement of animal use for eye-safety testing. ICCVAM evaluated and recommended the first two *in vitro* test methods that can now be used to determine whether substances can cause blindness and other severe eye damage, without the need for live animals (NIEHS 2008). Based on ICCVAM's evaluation, these test methods were adopted as international test guidelines in 2009.

In summary, ICCVAM has demonstrated its effectiveness and value in achieving the regulatory acceptance of test methods that reduce, refine, and replace animal use. Most importantly, by making appropriate science-based decisions, ICCVAM has ensured that such methods will continue to protect the public's health and safety. We expect ICCVAM to serve an increasingly important role in translating research advances into improved test methods that will benefit both people and animals.

The authors declare they have no competing financial interests.

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Polyethylene Terephthalate and Endocrine Disruptors

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In the commentary "Polyethylene Terephthalate May Yield Endocrine Disruptors," Sax (2010) theorized that bottles made of polyethylene terephthalate (PET) might leach phthalate ester plasticizers and/or antimony to produce endocrine-disrupting effects. On behalf of the North American producers of PET resin, I have the following comments and corrections.

Phthalate ester plasticizers are not used to manufacture polyethylene terephthalate and never have been. It is not chemically plausible for PET to produce these phthalate esters.

Sax (2010) did suggest that some reports of phthalate esters in PET bottled water containers may have originated from contamination of the bottled water, or from phthalate ester contamination of recycled PET used in manufacturing water and beverage containers. In addition, non-PET components of bottled water containers (e.g., closures) might be another possible source. Whatever the origin of phthalate esters, which could not be identified in any of the studies cited by Sax, it is clearly unreasonable to ascribe PET as the source.

Regarding antimony, Sax noted that Choe et al. (2003) reported antimony chloride as showing high estrogenicity. However, antimony oxides—not antimony chloride—are used as catalysts in the manufacture of PET. Antimony oxides are chemically and toxicologically distinct from antimony chlorides. No study has reported finding toxic amounts of antimony in PET-bottled water or beverages.

PET bottles and containers meet all applicable U.S. and international safety requirements for food contact, and the inert qualities of PET define its preferred use for many food, beverage, and medical applications. Consumers can feel confident about the safety of PET food and beverage containers.

We welcome dialogue with researchers and regulatory agencies on the chemistry and safety of PET resin.

The author is employed as the Executive Director of the PET Resin Association, the industry association representing North American producers of polyethylene terephthalate.

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